

A FACILE SYNTHESIS OF NEW 4-(PHENYLAMINO)THIENO[3,2-*d*]PYRIMIDINES USING 3-AMINOTHIOPHENE-2-CARBOXAMIDE

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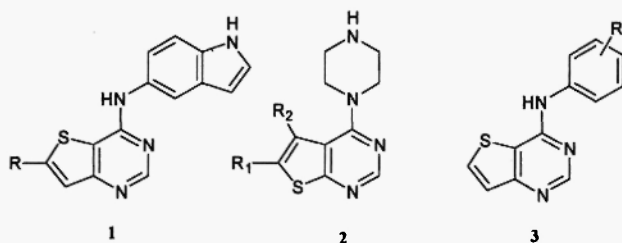
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Abstract: Several new 4-(phenylamino)thieno[3,2-*d*]pyrimidine derivatives **3** were synthesized in high yield by the reaction of aniline derivatives and 4-chlorothieno[3,2-*d*]pyrimidine that can be easily prepared using 3-aminothiophene-2-carboxamide.

Introduction

Thienopyrimidine derivatives have been found to have good medicinal and biological activities.¹ Recently, a novel class of thieno[3,2-*d*]pyrimidine **1** has been identified as potent inhibitors of VEGF receptor-2 kinase, which is a key component of the signaling pathway responsible for the sprouting and maturation of new blood vessels from tumors.² New thieno[2,3-*d*]pyrimidine derivatives **2** were also prepared and investigated as selective and potent ligands for the 5-HT₃ receptor.³ 5-HT₃ receptor ligands have potential therapeutic applications in the treatment of psychosis, memory impairment, and drugs abuse.⁴



Since a variety of thienopyrimidine derivatives are needed for their biological importance, we herein wish to report a facile method for the preparation of new 4-(phenylamino)thieno[3,2-*d*]pyrimidine derivatives **3** using 3-aminothiophene-2-carboxamide **4**⁵ in stead of methyl 3-aminothiophene-2-carboxylate.

Results and Discussion

The cyclization reaction of methyl 3-aminothiophene-2-carboxylate with formic amide was not efficient in forming **5** by previous known method.⁶ Yield of the product does not exceed 50% and the reaction needs two steps, a very high temperature and longer reaction time. We found a facile synthetic route to **3** started from the condensation reaction of 3-aminothiophene-2-carboxamide **4**⁵ with excess

boiling formic acid for 4 h to give thieno[3,2-*d*]pyrimidin-4(3*H*)-one **5** (mp 222-223°C)⁶ in 90% yield. The resultant **5** was easily converted in 2h to 4-chlorothieno[3,2-*d*]pyrimidine **6** (mp 123-124°C)⁶ using excess POCl₃. The conversion of **6** to the new 4-(phenylamino)thieno[3,2-*d*]pyrimidine derivatives **3** was accomplished by treatment with the appropriate aniline for 3-5 h in a mixture of 2-propanol/THF/HCl(trace) in high yields (85-95%) as shown Table-1.

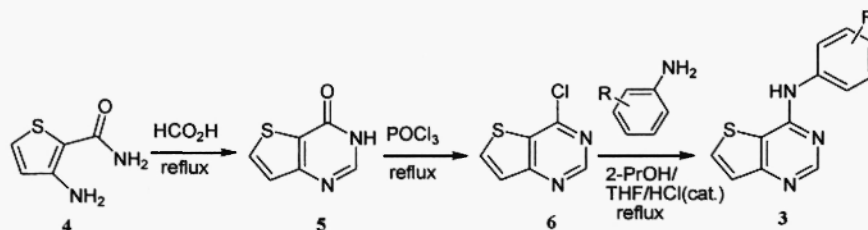


Table-1: 4-(Phenylamino)thieno[3,2-*d*]pyrimidine **3**^a

	R	isolated yield(%)	mp(°C)
3a ⁷	3'-Br	92	201-202
3b	H	88	186-188
3c	2'-CH ₃	90	220-221
3d	4'-Cl	95	101-102
3e	3'-I	85	139-140
3f	4'-OMe	91	155-157
3g	3',5'-diCl	92	167-169
3h	2,6'-diEt	90	65-67
3i	4'- <i>i</i> Pr	88	121-122

^a Satisfactory spectra for all new compounds were obtained in measurements of ¹H and ¹³C NMR and MS

References

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7. Compound **3a**: yield 92%; mp 201-202°C; ¹H NMR(300MHz, DMSO-*d*₆): δ 9.80(s, 1H, NH), 8.64(s, 1H, pyrimidine), 8.24(d, *J*=6.0 Hz, 1H, thiophene), 8.18(s, 1H, H-2'), 7.82(dd, 1H, H-4'), 7.48(d, *J*=6.0 Hz, 1H, thiophene), 7.30(t, 1H, H-5'), 7.25(dd, 1H, H-6'); ¹³C NMR: δ 115.8, 120.1, 121.2, 123.6, 124.4, 125.6, 130.6, 134.6, 141.0, 153.8, 154.8, 160.5; MS(*m/z*):306(*M*⁺).

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